

REMARKS

Claims 1-29 were pending in the application. Claims 30-48 are withdrawn. Claim 29 has been amended. Upon entry of these amendments, Claims 1-29 will be pending and under active consideration. Claims 1, 23, and 29 are independent.

In compliance with Examiner's request, Claims 30-48 are withdrawn from consideration without prejudice to pursuing the withdrawn subject matter in this or other continuation or divisional applications.

Applicants submit respectfully that the amendments presented herein are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter.

Claim 29 is amended herein to recite "a housing comprising an inner side comprising: a gas introduction means integral to the housing and a gas expiration means integral to the housing." The amendment is supported fully by the claims and/or specification as originally filed and, thus, does not represent new subject matter. In particular, the amendment to Claim 29 finds support at page 12, lines 13-35.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Office Action, at pages 2-3, rejects Claims 1-4, 8-13, 18, 21, and 29 as allegedly being anticipated by U.S. Patent No. 5,015,585 to Robinson (hereinafter,

"Robinson"), under 35 U.S.C. § 102(b) for the reasons of record. In sum, the Office Action alleges that Robinson discloses a bioreactor, allegedly as described in the present application, with a housing having nutrient inlets and outlets that allow nutrient solutions to pass therethrough and an array of coaxial semipermeable fibers defining compartments within the innermost fiber, between the innermost fiber and the outermost fiber, and outside the outermost fiber. The Office Action alleges further that nutrient solutions serve as an extracellular matrix by providing nutrients required for cell homeostasis, and may contain oxygen. The Office Action alleges that the bioreactor illustrated in FIG. 1 has a hollow tube 17 cm long and a pore size of 0.2 microns, allegedly falling within the range claimed by Applicants. With regard to Applicants' claim drawn to the method of sterilization of the bioreactor, the Office Action alleges that such a limitation amounts to a recitation of the intended use of the device and does not patentably distinguish the present device from the prior art. Applicants traverse respectfully.

Applicants submit respectfully that Claims 1-4, 8-13, 18, 21, and 29 are not anticipated by Robinson because Robinson does not disclose each and every element of those claims as is required for a *prima facie* showing of anticipation. In particular, Claim 1, from which Claims 2-4, 8-13, 18, and 21 depend, and Claim 29, as amended, are directed to a bioreactor, comprising a housing having an inner side further comprising a gas introduction means integral to the housing and a gas expiration means integral to the housing. As noted in the Office Action, the Robinson device provides that a nutrient solution passes through the innermost porous hollow fiber and through the outermost chamber, allowing the nutrients to mix diffusively with eukaryotic cells in the

space between. As further noted in the Office Action, Robinson provides that the nutrient solution may contain oxygen. Applicants submit respectfully that Robinson does not teach or suggest a gas introduction means integral to the housing and a gas expiration means integral to the housing as claimed by Applicants.

As disclosed, for example, at page 14, lines 23-34, page 20, lines 14-36, and in FIG. 2B, of the present specification, Applicants' claimed invention comprises an integral aeration system whereby the nutrient solution flowing through Applicants' device is supplied constantly with gasses such as oxygen. In contrast, Robinson's device requires that the nutrient solution be oxygenated prior to entry into the device, and thus the nutrient solution may become depleted of oxygen during its course through the device. Accordingly, Applicants submit respectfully that Applicants' claimed device operates on a substantially different principle from the Robinson device with regard to oxygenation of the nutrient solution, and Applicants' claimed invention differs patentably from the Robinson device by providing integral gas introduction and expiration means within the housing.

In light of the above, Applicants submit respectfully that the claims of the present invention, as amended, are not anticipated by Robinson and that the rejection to Claims 1-4, 8-13, 18, 21, and 29 under 35 U.S.C. § 102(b) has been overcome. Accordingly, Applicants request respectfully that the rejection to Claims 1-4, 8-13, 18, 21, and 29 under 35 U.S.C. § 102(b) be withdrawn.

II. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. The Rejections Over Robinson Alone Or In View Of Naughton

The Office Action, at pages 2-5, rejects Claims 5-7, 14-15, 19-20, and 22-28 as allegedly being obvious over Robinson either alone or in view of U.S. Patent No. 6,218,182 to Naughton *et al.* (hereinafter, "Naughton"), under 35 U.S.C. § 103(a) for the reasons of record. The Office Action alleges, in sum, that Robinson teaches all the limitations of the rejected claims with respect to the apparatus with the exception of using liver cells, the number of cells in the reactor, and the pore size of the fibers, but that those deficiencies are allegedly cured through obvious modification. With respect to Claims 15, 22, and 28, the Office Action acknowledges that Robinson does not disclose treatment of a patient, but that this deficiency in Robinson is cured by Naughton. Applicants traverse respectfully.

Without acquiescing in the arguments presented by the Office Action, Applicants submit respectfully that the novel devices and methods of the present invention are neither taught nor suggested by Robinson, either alone or in view of Naughton. There is neither teaching nor suggestion in these references that the device include integral aeration means, such as the integral gas inlets and outlets of the present invention as claimed. As noted above, Robinson neither teaches nor suggests such integral aeration means, and the Office Action does not assert either that such integral aeration would be obvious over Robinson alone or that Naughton cures this deficiency. In fact, by teaching that the nutrient solution may be oxygenated prior to entry into device (see for example, Robinson at Column 6, lines 16-22), Robinson effectively teaches away from an integral oxygenation system. Thus, Applicants submit respectfully that, as neither

Robinson alone nor the combination with Naughton cure the deficiencies of Robison with respect to the integral aeration means of the present invention, neither Robinson alone nor the combination of Robinson with Naughton meets the threshold required for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

Accordingly, Applicants submit respectfully that the rejection of Claims 5-7, 14-15, 19-20, and 22-28 under 35 U.S.C. § 103(a) have been overcome, and Applicants request respectfully that the rejection of Claims 5-7, 14-15, 19-20, and 22-28 under 35 U.S.C. § 103(a) be withdrawn.

B. The Rejection Over Robinson And Naughton In View Of Stephanopoulos

The Office Action, at pages 5, rejects Claims 16 and 17 as allegedly being obvious over Robinson in view of Naughton and further in view of U.S. Patent No. 5,510,262 to Stephanopoulos *et al.* (hereinafter, "Stephanopoulos"), under 35 U.S.C. § 103(a) for the reasons of record. The Office Action alleges, in sum, that Robinson and Naughton teach Applicants' claimed device with the exception of aeration and perfluorocarbon coating on the microfiber growth area, and that Stephanopoulos cures this deficiency. Applicants traverse respectfully.

While admitting that Robinson in view of Naughton is deficient with respect to Applicant's claimed invention, the Office Action alleges that Stephanopoulos cures those deficiencies by teaching a hollow fiber cell culture device wherein the medium is aerated by containment in a growth medium reservoir and that perfluorocarbon may be added to the medium to increase the oxygen solubility in the growth medium. Without

acquiescing in the propriety of the allegation that Robinson in view of Naughton and further in view of Stephanopoulos teaches such a combination, Applicant submits respectfully that Stephanopoulos may not properly be combined with Robinson and Naughton to reach Applicant's claimed invention because Robinson, as noted above, teaches away from the modification of Stephanopoulos (*i.e.*, teaches away from an integral aeration system by providing a nutrient medium that is oxygenated prior to entry into the bioreactor). A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). It is improper to combine references where the references teach away from their combination. In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). Accordingly, Applicants submit respectfully that the deficiencies of Robinson in view of Naughton with respect to Applicant's claimed invention cannot be cured by Stephanopoulos because Stephanopoulos cannot be combined permissibly with Robinson and Naughton.

Even further, Applicants submit respectfully that the teachings of Stephanopoulos, even if Stephanopoulos could be combined permissibly with Robinson in view of Naughton, would not cure Robinson's deficiencies. As alleged in the Office Action, Stephanopoulos teaches a hollow fiber cell culture device wherein the medium is aerated by containment in a growth medium reservoir, from which the nutrient medium

is circulated into the bioreactor, and that perfluorocarbon may be added to the medium to increase the oxygen solubility in the growth medium. Applicants' claimed invention does not comprise a separate growth medium reservoir for the aeration of the growth medium. Instead, the aeration occurs within the bioreactor itself and occurs by diffusion rather than by injection, as in the Stephanopoulos device. Furthermore, Applicants' use of perfluorocarbon occurs at the microfiber itself rather than in a separate growth medium reservoir, as in the Stephanopoulos device. Thus, Applicants submit respectfully that these aspects of the Stephanopoulos device are patentably distinct from Applicants' claimed invention and cannot cure the deficiencies of Robinson and Naughton.

Accordingly, Applicants submit respectfully that the rejection of Claims 16 and 17 under 35 U.S.C. § 103(a) has been overcome, and Applicants request respectfully that the rejection of Claims 16 and 17 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants submit respectfully that the present application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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